High-frequency percussive ventilation and low tidal volume ventilation in burns: A randomized controlled trial*

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Objectives: **In select burn intensive care units, high-frequency percussive ventilation is preferentially used to provide mechanical ventilation in support of patients with acute lung injury, acute respiratory distress syndrome, and inhalation injury. However, we found an absence of prospective studies comparing high-frequency percussive ventilation with contemporary low-tidal volume ventilation strategies. The purpose of this study was to prospectively compare the two ventilator modalities in a burn intensive care unit setting.**

Design: **Single-center, prospective, randomized, controlled clinical trial, comparing high-frequency percussive ventilation with low-tidal volume ventilation in patients admitted to our burn intensive care unit with respiratory failure.**

Setting: **A 16-bed burn intensive care unit at a tertiary military teaching hospital.**

Patients: **Adult patients ≥18 yrs of age requiring prolonged (>24 hrs) mechanical ventilation were admitted to the burn intensive care unit. The study was conducted over a 3-yr period between April 2006 and May 2009. This trial was registered with ClinicalTrials.gov as NCT00351741.**

Interventions: **Subjects were randomly assigned to receive mechanical ventilation through a high-frequency percussive ventilation-based strategy (n = 31) or a low-tidal volume ventilation-based strategy (n = 31).**

Measurements and Main Results: **At baseline, both the high-frequency percussive ventilation group and the low-tidal volume ventilation group had similar demographics to include median age (interquartile range) (28 yrs [23–45] vs. 33 yrs [24–46], p = nonsignificant), percentage of total body surface area burn (34 [20–52] vs. 34 [23–50], p = nonsignificant), and clinical diagnosis of inhalation injury (39% vs. 35%, p = nonsignificant). The primary outcome was ventilator-free days in the first 28 days after randomization. Intent-to-treat analysis revealed no significant difference between the high-frequency percussive ventilation and the low-tidal volume ventilation groups in mean (± SD) ventilator-free days (12 ± 9 vs. 11 ± 9, p = nonsignificant). No significant difference was detected between groups for any of the secondary outcome measures to include mortality except the need for "rescue" mode application (p = .02). Nine (29%) in the low-tidal volume ventilation arm did not meet predetermined oxygenation or ventilation goals and required transition to a rescue mode. By contrast, two in the high-frequency percussive ventilation arm (6%) required rescue.**

Conclusions: **A high-frequency percussive ventilation-based strategy resulted in similar clinical outcomes when compared with a low-tidal volume ventilation-based strategy in burn patients with respiratory failure. However, the low-tidal volume ventilation strategy failed to achieve ventilation and oxygenation goals in a higher percentage necessitating rescue ventilation. (Crit Care Med 2010; 38:1970–1977)**

KEY WORDS: burns; high frequency; percussive ventilation; low-tidal volume ventilation; inhalation injury

Respiratory failure in the setting of concomitant severe burn presents a variety of challenges that call for innovative therapeutic options. Inhalation of the products of combustion imparts airway and lung parenchymal damage known as inhalation injury, a condition that affects up to 15% of burn patients. The injury results in tracheobronchial mucosal edema, sloughing, and hemorrhage and carries a substantially increased attributable risk of pulmonary infection and patient mortality (1–3). Even in the absence of inhalation injury, decreased chest wall compliance early from full-thickness burns or resuscitation-related edema, and later from scar and contracture formation, may make it difficult to achieve clinically adequate gas exchange.

High-frequency percussive ventilation (HFPV) is a pneumatically driven, pressure-limited, time-cycled mode of ventilation that delivers high-frequency (≥300 subtidal breaths/minute or 5 Hz) bursts of gas superimposed on a biphasic in-

***See also p. 2069.**

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spiratory and expiratory pressure cycle set at 10–15 cycles per minutes (4–6). After inhalation injury, the percussive air flow delivered by HFPV is believed to facilitate evacuation of debris originating from epithelial sloughing, hemorrhage, and inflammation. A number of case–control studies demonstrated a decrease in the incidence of ventilator-associated pneumonia (VAP) in patients with inhalation injury when supported with HFPV compared with conventional modes of ventilation (1, 7, 8). Thus, this mode is favored in some burn centers for the management of inhalation injury. When compared with conventional ventilation, HFPV has been shown to improve gas exchange at lower peak and mean airway pressures in various patient populations (4, 9–11). To date, only one prospective randomized controlled trial has been performed in adult burn patients involving 35 subjects with inhalation injury, which demonstrated improved oxygenation early but no difference in pulmonary infection or mortality (12).

In the last decade, lung-protective low-tidal volume conventional ventilation (LTV) has led to an improvement in clinical outcomes among patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) (13). This strategy has been widely extrapolated to patients without ALI/ARDS (14). However, the benchmark studies that defined the LTV approach largely excluded burned patients from enrollment. In addition, the earlier studies of HFPV vs. conventional ventilation were conducted during the era before LTV. It is unclear whether the LTV strategy can be effectively applied in patients with severe burns with or without inhalation injury. We therefore conducted a prospective randomized controlled trial to determine whether HFPV would improve clinical outcomes in comparison to LTV.

MATERIALS AND METHODS

Patients. After obtaining approval from the local Institutional Review Board, we conducted a prospective, randomized clinical trial in a 16-bed burn intensive care unit located in a tertiary military teaching hospital. All adult patients ≥18 yrs of age admitted to our burn intensive care unit who were intubated and placed on mechanical ventilation were eligible for enrollment if they had an anticipated need of >24 hrs of continued ventilatory support. Patients who were not intubated at the time of admission but later intubated during their hospitalization were also eligible for the study. Reasons for exclusion were pregnancy, no expectation of survival of >24 hrs, prisoner status, and traumatic brain injury requiring intracranial pressure monitoring.

Patients who met inclusion and exclusion criteria were identified and surrogate decisionmakers contacted for written informed consent. Once consent was obtained, subjects were randomized by paired grouping by age (≥65 or <65 yrs) and by clinical diagnosis of inhalation injury. A random drawing of a sealed envelope revealed the study arm and subsequent subjects enrolled within that same group were placed in the opposite study arm. After each complete pair, a new drawing was performed.

Each patient underwent fiberoptic bronchoscopy within the first 24 hrs of burn intensive care unit admission for diagnosis of inhalation injury. Diagnostic findings on bronchoscopy included carbonaceous debris below the vocal cords, mucosal erythema, and/or ulceration. Other standard practices during the study period included resuscitation of all patients with >20% total body surface area burns using the modified Brooke formula (15) to determine the initial fluid rate with subsequent titration of intravenous fluids to sustain a 30 to 50 mL/hr urine output. All subjects with full-thickness burn wounds underwent early excision (<7 days after burn) and skin grafting, application of topical antimicrobials, and implementation of standardized infection control protocols. Ventilator mode before study enrollment was determined by the admitting surgeon.

Ventilator Procedures. Subjects were placed on the study ventilation mode within 1 hr of randomization. Those randomized to the HFPV arm were placed on the VDR-4 (Percussionaire, Sandpoint, ID) and managed using an algorithm, which continued until liberation from the ventilator, rescue mode intervention, at least 28 days for persistent ventilator support, or death (see Supplemental Fig. 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A158]). Those randomized to the LTV arm were placed on volume-limited assist-control ventilation using a low-tidal volume algorithm adapted and modified from the ARDSnet study (13) (see Supplemental Fig. 2 [Supplemental Digital Content 1, http://links.lww.com/CCM/A158]). The tidal volume was set at 6 mL/kg of predicted body weight and reduced further by 1 mL/kg, if necessary, to maintain a plateau pressure of <30 cm H_2O. Subjects in this arm were also continued until liberation from the ventilator, rescue mode intervention, at least 28 days of persistent ventilator support, or death.

Ventilator Rescue. Subjects who did not meet predetermined oxygenation and ventilation goals on the study mode despite ventilator-specific optimization were switched to a rescue mode of ventilation. Either HFPV using the VDR-4 or airway pressure release ventilation using the EVITA XL (Dräger Medical Inc, Telford, PA) were considered for "rescue" based on clinician preference (see Supplemental Figs. 3 and 4 for the airway pressure release ventilation algorithm and method of weaning [Supplemental Digital Content 2, http://links.lww.com/CCM/A159]). Criteria for changing modes were as follows: severe hypoxemia with arterial partial pressure of oxygen (Pa_{O_2}) <60 mm Hg despite a positive end-expiratory pressure >20 cm H_2O on the LTV mode or a peak inspiratory pressure >50 cm H_2O on the HFPV mode at an F_{IO_2} of 100% for >1 hr; severe hypercapnia with arterial partial pressure of carbon dioxide (Pa_{CO_2}) >70 mm Hg along with an arterial pH <7.2 despite optimization of minute ventilation; or development of ventilator-associated tracheobronchitis (VATB) (16). Use of other adjuncts before rescue such as induction of chemical paralysis, recruitment maneuvers, prone positioning, or initiation of inhaled nitric oxide was determined by the attending physician on a case-by-case basis.

Ventilator Weaning. Ventilator liberation, defined as extubation or the disconnection of a patient's tracheostomy tube from mechanical ventilator support for 48 consecutive hrs, was standardized in both arms using a mode-specific weaning protocol (see Supplemental Figs. 5 and 6 [see Supplemental Digital Content 1, http://links.lww.com/CCM/A158]). The liberation protocol included daily sedation holidays and respiratory therapy-guided liberation protocols supplemented by spontaneous breathing trials (see Supplemental Fig. 7 [see Supplemental Digital Content 3, http://links.lww.com/CCM/A160]).

Compliance with specific algorithms was monitored on a daily basis by the principal investigator (KKC) along with the research staff. Incidents of protocol noncompliance were recorded as protocol deviations or violations and reported to the Institutional Review Board.

Data Collection. Patient demographic data as well as total body surface area, percent full-thickness burn, diagnosis of inhalation injury, Injury Severity Score, diagnosis of ALI/ARDS using the standard criteria (17), and the number of ventilator days before randomization were recorded within 24 hrs of randomization. Except where stated otherwise, all patient and ventilator parameters were recorded daily until 28 days after randomization.

End Points. The primary end point was ventilator-free days in the first 28 days, defined as the number of days after randomization from day 0 to day 28 alive without ventilator assistance for at least 48 consecutive hrs. Secondary end points were identified as follows: 28-day mortality; days free from nonpulmonary organ failure as adapted from the ARDSnet study (13); VAP as defined by the American Thoracic Society and the Infectious Disease Society of America (18); barotrauma as defined as a new pneumothorax, pneumomedi-

astinum, subcutaneous emphysema, interstitial emphysema, or pneumatocele >2 cm in diameter not associated with a vascular procedure, lung biopsy, or thoracentesis; VATB as defined as carinal or mainstem airway friability and sloughing with associated bleeding; need for rescue mode; and death before 28 days after randomization. Notably, VATB was only diagnosed after the patient had spent at least 7 days on the assigned ventilator mode and had not been diagnosed with inhalation injury on admission (16). Additional secondary outcome measures included the ratio of Pao_2 to Fio_2 and the oxygenation index in the first 7 days after randomization. Oxygenation index was defined as the product of the Fio_2 in percent and mean airway pressure in cm H_2O divided by the Pao_2.

Plasma Cytokine Concentrations. For each subject, immunoassays for interleukin (IL)-1β, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α were performed using a human inflammatory five-plex assay kit (Biosource International, Inc, Camarillo, CA) and analyzed on a Luminex 100 luminescent analyzer (Luminex Corp, Austin, TX) on days 0, 3, and 7. Each sample was measured in duplicate and averaged. Greater than 90% of values resulted for IL-1β, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α fell below the lower limit of quantitation and thus were not further analyzed.

Statistical Analysis. In 2004, institutional performance improvement data revealed that the average ventilator days per patient stay was 13 ± 7 in our burn intensive care unit. Based on these data, sample size of 170 subjects (85 in each arm) was calculated to detect an absolute difference of 2 ventilator days between the two groups to achieve 80% power and two-sided $\alpha = 0.05$. One interim analysis was planned after either 50% enrollment was achieved or after 3 yrs had passed since beginning enrollment. It was predetermined that enrollment would be stopped if significance was achieved in the primary end point. It was also predetermined, for safety reasons, that enrollment would be stopped if 30% of subjects in one arm needed to switch to a rescue mode.

For continuous variables, all data are presented as mean ± SD or median with interquartile range. Continuous data were analyzed using two-tailed Student's *t* test or Mann-Whitney *U* test when appropriate. Categorical data were analyzed with chi-square or Fisher's exact tests when appropriate. Statistical significance was set at $p < .05$. Where appropriate, repeated-measures analysis of variance was performed to assess for differences over time within the same group as well as differences between groups over time. Comparisons of primary and secondary end points between the two groups were performed according to the intention-to-treat principle. All data were analyzed with SAS version 9.1 (SAS Institute, Cary, NC).

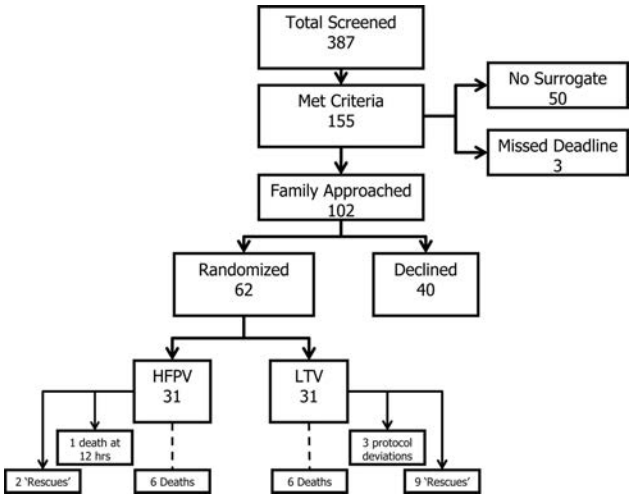


Figure 1. CONSORT diagram.

RESULTS

After 3 yrs of enrollment, interim analysis revealed a significant number of subjects in the LTV arm required rescue, which served as the trigger to close the study to further enrollment. Between April 2006 and May 2009, 387 patients were screened for eligibility. Of these, 155 patients met criteria of which 62 were randomized, 31 to the HFPV arm and 31 to the LTV arm (Fig. 1). Subjects in both groups received mechanical ventilator support a median of 2 (1–3) days before randomization into the study. There were no statistically significant differences in demographics, total body surface area burned, percent full thickness burned, or diagnosis of inhalation injury at the time of enrollment (Table 1).

Table 1. Baseline characteristics of study subjects

	HFPV (n = 31)	LTV (n = 31)	*p*
Age[a]	28 (23–45)	32 (24–45)	NS
Sex	87% males	84% males	NS
Combat-injured, no.(%)	14 (45)	14 (45)	NS
Percent TBSA[a]	34 (21–51)	35 (24–50)	NS
Percent FT[a]	14 (4–26)	16 (8–31)	NS
Inhalation, no. (%)	12 (39)	11 (35)	NS
ISS	25 (16–34)	25 (16–34)	NS
ALI/ARDS, no. (%)	12 (39)	14 (45)	NS
Prior ventilator days	2 (1–3)	2 (1–3)	NS

HFPV, high-frequency percussive ventilation; LTV, low-tidal volume ventilation; TBSA, total body surface area burned; FT, full thickness burned; ISS, Injury Severity Score; ALI/ARDS, acute lung injury/acute respiratory distress syndrome; NS, nonsignificant.

[a]Median (interquartile range, 1–3).

A detailed description of ventilator characteristics during the first week after randomization is provided in Table 2. Peak inspiratory pressures were significantly lower in the HFPV arm when compared with the LTV arm during the first 5 days after randomization. There was no significant difference in the daily mean airway pressures over the first week noted between the two arms. Over the 28-day study period, 90% of all recorded tidal volumes were <8 mL/kg as dictated by the LTV algorithm, whereas 87% of all recorded plateau pressures were <30 cm H_2O.

Overall, ventilator-free days in the first 28 days were no different between the HFPV arm and the LTV arm (12 ± 9 vs. 11 ± 9, *p* = nonsignificant) (Table 3). Of the secondary end points, the number of patients requiring rescue (two [6%] vs. nine [29%], $p = .02$) and the number who developed barotrauma (zero [0%] vs. four [13%], $p = .04$) were significantly different between HFPV and LTV. There was a trend toward those in the HFPV arm having less VAP than the LTV arm (10 [32%] vs. 16 [52%], $p = .12$).

After randomization, nine met criteria for rescue and switched to either airway pressure release ventilation or HFPV for profound hypoxemia (n = 5) or for profound hypercapnia (n = 4). Three subjects in the LTV arm were switched to airway pressure release ventilation with-

Table 2. Ventilator characteristics for each arm 0, 3, and 7 days after randomization

	Day 0		Day 3		Day 7	
	HFPV	LTV	HFPV	LTV	HFPV	LTV
Tidal volume, mL/kg (no.)	—	6.2 ± 1.0 (24)	—	6.5 ± 1.2 (21)	—	6.4 ± 1.3 (7)
PIP, cm H_2O (no.)	26 ± 4 (27)	32 ± 10 (24)[a]	28 ± 8 (24)	40 ± 11 (22)[a]	27 ± 10 (10)	33 ± 13 (6)
Pulse frequency, subtidal breaths/min (no.)	562 ± 33 (26)	—	572 ± 74 (19)	—	580 ± 94 (15)	—
Plateau pressure, cm H_2O (no.)	—	23 ± 9 (16)	—	29 ± 8 (15)	—	31 ± 14 (5)
Total CPAP+/PEEP, cm H_2O (no.)	10 ± 1 (20)	7 ± 3 (29)[a]	11 ± 2 (20)	10 ± 5 (25)	11 ± 2 (19)	10 ± 7 (10)
Mean airway pressure, cm H_2O (no.)	18 ± 6 (20)	16 ± 9 (27)	20 ± 10 (18)	21 ± 8 (22)	20 ± 10 (9)	16 ± 5 (7)
Respiratory rate (no.)	22 ± 8 (27)	22 ± 8 (29)	28 ± 10 (20)	29 ± 7 (25)	21 ± 6 (10)	25 ± 9 (10)
Minute ventilation, L/min (no.)	—	10 ± 4 (23)	—	12 ± 6 (20)	—	14 ± 7 (9)
pH (no.)	7.34 ± 0.05 (30)	7.30 ± 0.11 (28)	7.34 ± 0.11 (22)	7.33 ± 0.10 (27)	7.36 ± 0.08 (17)	7.37 ± 0.07 (15)
$Paco_2$, mm Hg (no.)	44 ± 7 (30)	52 ± 10 (28)[a]	51 ± 12 (22)	54 ± 14 (27)	49 ± 16 (17)	45 ± 9 (15)
Pao_2, mm Hg (no.)	135 ± 77 (30)	93 ± 36 (28)[a]	94 ± 81 (22)	85 ± 25 (27)[a]	92 ± 23 (17)	95 ± 29 (15)
Fio_2, % no.	46 ± 23 (30)	54 ± 20 (28)[a]	56 ± 29 (22)	53 ± 20 (27)	51 ± 28 (17)	49 ± 21 (15)
PFR (no.)	368 ± 128 (30)	258 ± 117 (28)[a]	285 ± 109 (22)	213 ± 95 (27)[a]	268 ± 131 (17)	255 ± 103 (15)
OI (no.)	9 ± 16 (20)	10 ± 9 (27)	7 ± 5 (18)	12 ± 7 (22)[a]	6 ± 4 (9)	11 ± 7 (7)

HFPV, high-frequency percussive ventilation; LTV, low-tidal volume ventilation; PIP, peak inspiratory pressure; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; PFR, Pao_2/Fio_2 ratio; OI, oxygenation index.

[a]$p < .05$ when compared with HFPV. For subjects on the HFPV, total CPAP is a sum of the oscillatory PEEP and the demand PEEP.

Table 3. Main outcome variables

	HFPV (n = 31)	LTV (n = 31)	p
Ventilator-free days[a]	12 ± 9	11 ± 9	NS
Days free from nonpulmonary organ failure[a]	15 ± 11	15 ± 10	NS
Death, no. (%)	6 (19)	6 (19)	NS
Rescue, no. (%)	2 (6)	9 (29)	.02
VAP, no. (%)	10 (32)	16 (52)	NS
VATB, no. (%)	2 (6)	0	NS
Barotrauma, no. (%)	0 (0)	4 (13)	.04

HFPV, high-frequency percussive ventilation; LTV, low-tidal volume ventilation; VAP, ventilator-associated pneumonia; VATB, ventilator-associated tracheobronchitis; NS, nonsignificant.

[a]Mean ± SD.

Table 4. Comparison of subgroup of patients with inhalation injury

	HFPV (n = 12)	LTV (n = 11)	p
Ventilator-free days[a]	9 ± 7	9 ± 10	NS
Days free from nonpulmonary organ failure[a]	11 ± 11	13 ± 10	NS
Death, no. (%)	3 (25)	3 (27)	NS
Rescue, no. (%)	0 (0)	7 (64)	.001
VAP, no. (%)	6 (50)	7 (64)	NS
Barotrauma, no. (%)	0 (0)	2 (18)	NS

HFPV, high-frequency percussive ventilation; LTV, low-tidal volume ventilation; VAP, ventilator-associated pneumonia; NS, nonsignificant.

[a]Mean ± SD.

out meeting predetermined rescue criteria and were not counted as a true "rescue." Two subjects in the HFPV were switched to airway pressure release ventilation after meeting the criteria for VATB. Among the five subjects in the LTV requiring rescue for profound hypoxemia, the mean ratio of Pao_2 to Fio_2 was 58 ± 6 with a mean positive end-expiratory pressure of 22 ± 2 cm H_2O before rescue. Two of these patients were paralyzed, received inhaled nitric oxide, and were placed in the prone position before rescue. Among the four subjects requiring rescue for hypercapnia, the mean pH was 7.18 ± 0.04 with a mean $Paco_2$ of 80 ± 14 mm Hg before rescue. Six of nine rescues occurred within 7 days after randomization to the LTV arm. Two patients died despite rescue, one within the first 7 days and another at day 20, both secondary to multiple organ failure. In an *a priori* subgroup analysis of patients with inhalation injury (n = 23), 64% of subjects in the LTV arm required rescue, whereas none of the HFPV needed rescue ($p = .001$) (Table 4). Table 5 lists ventilator and arterial blood gas characteristics of all rescue subjects. Both of the subjects in the HFPV arm who developed VATB demonstrated normalization of the mucosa after 24 hrs on the alternate mode.

The ratio of Pao_2 to Fio_2 was significantly better in the HFPV arm on days 0, 1, 2, and 3 when compared with the LTV arm (Fig. 2). This difference was not sustained after 4 days. Furthermore, when comparing oxygenation index, there was no difference detected between the two groups or over time.

Sedation requirements trended lower in the HFPV arm compared with the LTV arm with both the median (interquartile range) total dose of lorazepam in the first 7 days (29 [21–56] mg vs. 55 [31–76] mg) or 28 days (54 [27–96] mg vs. 80 [41–135] mg). However, these comparisons did not reach statistical significance ($p = .11$ and .18, respectively).

Mean plasma interleukin-6 and interleukin-8 levels (pg/mL) at days 0, 3, and 7 were no different over time within the same group or between the two groups on repeated-measures analysis of variance (Fig. 3).

DISCUSSION

To the best of our knowledge, this is the first study to compare, in a randomized controlled fashion, HFPV to a low-tidal volume strategy in severely burned adult patients. By the intent-to-treat principle, there was no detectible difference in the primary end point of ventilator-free days in the first 28 days between a HFPV group and a LTV group. Even if the study had continued until target en-

Table 5. Ventilator and arterial blood gas characteristics of subjects requiring rescue

No.	Study Mode	Rescue Mode	Criteria	Day[a]	TV	RR	PEEP	Pl	Fio_2	pH	$Paco_2$	Pao_2	Outcome
1	LTV	APRV	Hypoxemia	4	5.3	34	24	36	100	7.21	65	57	Lived
2	LTV	APRV	Hypoxemia	5	4.5	30	20	32	100	7.35	54	50	Died on day 20
3	LTV	APRV	Hypoxemia	11	7.2	38	20	33	100	7.18	55	63	Lived
4	LTV	APRV	Hypoxemia	12	5.5	36	24	34	100	7.28	67	54	Lived
5	LTV	APRV	Hypoxemia	4	6.5	30	20	37	100	7.05	83	64	Lived
6	LTV	HFPV	Hypercapnia	13	6.2	40	5	28	80	7.16	61	105	Lived
7	LTV	APRV	Hypercapnia	3	7.1	36	10	37	60	7.23	76	145	Lived
8	LTV	HFPV	Hypercapnia	5	7.1	30	10	37	100	7.15	92	78	Lived
9	LTV	HFPV	Hypercapnia	5	7.5	30	8	38	40	7.18	89	90	Died on day 7

No.	Study Mode	Rescue Mode	Criteria	Day[a]	PF	PIP	RR	$CPAP_t$	Fio_2	pH	$Paco_2$	Pao_2	Outcome
1	HFPV	APRV	VATB	5	800	30	20	10	50	7.29	47	75	Died on day 15
2	HFPV	APRV	VATB	4	700	22	15	10	30	7.33	58	74	Lived

TV, tidal volume in milliliters per kilogram; RR, respiratory rate per minute; PEEP, positive end-expiratory pressure (cm H_2O); Pl, plateau pressure (cm H_2O); LTV, low-tidal volume ventilation; APRV, airway pressure release ventilation; HFPV, high-frequency percussive ventilation; PF, pulse frequency (subtidal breath/minute); PIP, peak inspiratory pressure (cm H_2O); VATB, ventilator-associated tracheobronchitis; CPAPt, total continuous positive airway pressure (cm H_2O).

[a]Number of days after randomization. All values represented are those obtained no more than 1 hr before rescue.

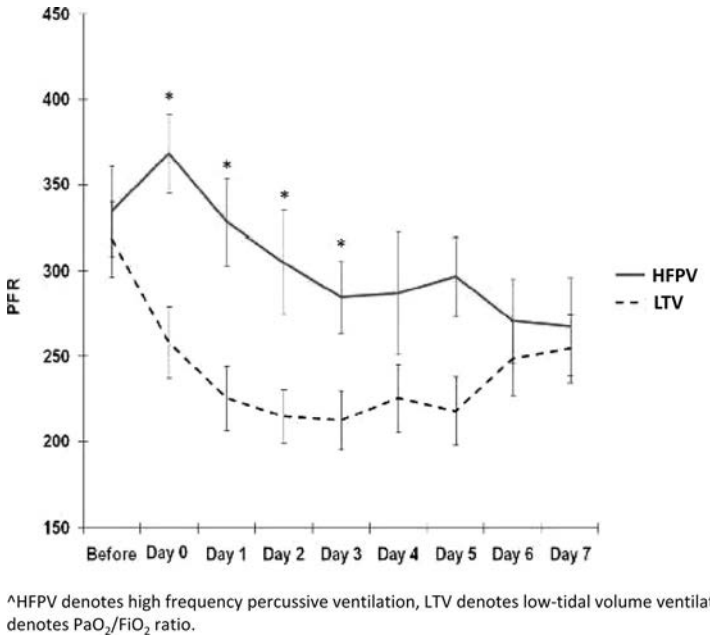
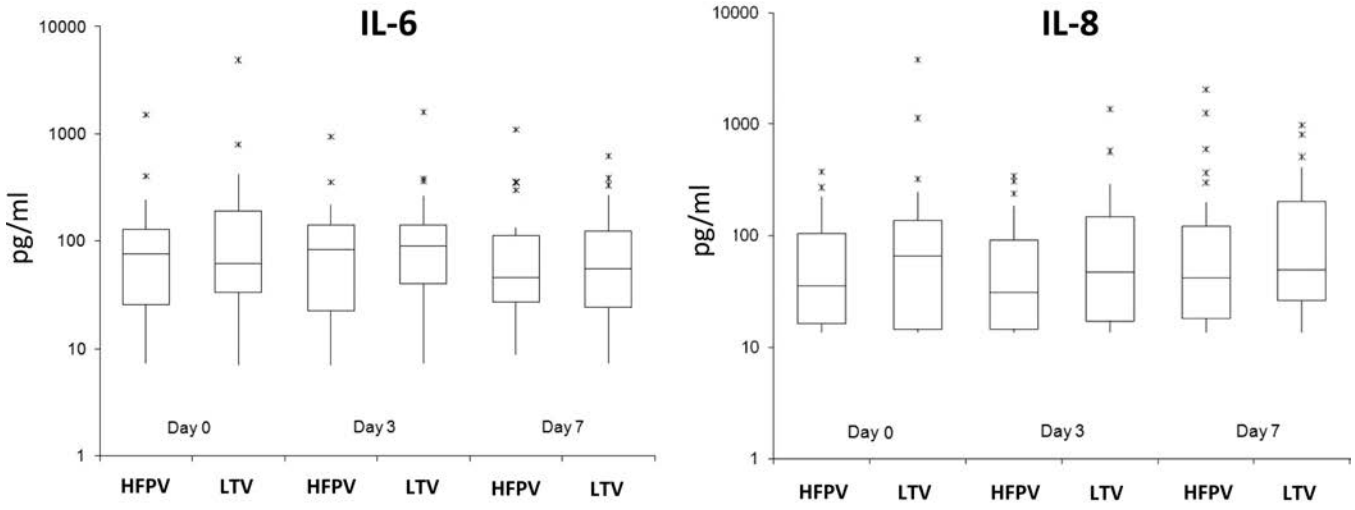


Figure 2. Comparison of the ratio of the partial pressure of arterial oxygen (Pao_2) to fraction of inspiratory oxygen (Fio_2). Data points are depicted as mean±SEM *$p < .05$.

rollment, it is unlikely that a significant difference would have been detected. Among our secondary end points, need for rescue was significantly higher in the LTV arm with 29% of the subjects unable to meet oxygenation and ventilation goals despite optimization of the study mode. In a subgroup of patients with inhalation injury, 64% (seven of 11 subjects) in the LTV arm required rescue. Thus, the majority of rescue patients were those with inhalation injury. Based on these findings on interim analysis, the decision was made to stop the trial for safety concerns.

Over the last decade, application of the "first do no harm" principle in the form of a lower tidal volume strategy in the management of ALI/ARDS has been one of the important advances in critical care (3, 13). Abundant experimental and clinical studies have demonstrated the beneficial effects of an LTV strategy on volutrauma and barotrauma (13, 19–25). In clinical practice, the LTV strategy has been extrapolated to patients without ALI (14, 26). Determann et al (27), in a preventive randomized trial, recently demonstrated that mechanical ventilation with tidal volumes of 6 mL/kg in critically ill patients without ALI/ARDS was associated with a decrease in the incidence of lung injury (2.6% vs. 13.5%) when compared with 10 mL/kg tidal volumes. Higher tidal volumes were also associated with sustained cytokine production as measured in plasma in the form of IL-6 levels.

Based on our findings, it appears strict application of a LTV strategy may be suboptimal in the burn population, particularly in those with inhalation injury. Meeting oxygenation and ventilation goals in patients with severe burns can be challenging. The presence of noncompliant thoracic and abdominal eschar before excision and grafting and subsequent circumferential extrathoracic placement of wound dressings make it difficult to interpret plateau pressures to guide a lung-protective strategy. The considerable volume of fluids needed to resuscitate patients with large burns has been well described previously (28–30). A recent report by our group demonstrated a requirement of up to a mean of 25 ± 11 L in the first 24 hrs alone for an average burn size of 50% total body surface area (29). Edema secondary to massive burn resuscitation compounds the extrapulmonary impediment to lung excursion. The presence of inhalation injury further



*Samples from 31 subjects in each group in picogram/milliliter are plotted on a logarithmic graph. No significance was found on repeated measures analysis of variance over time within groups or between groups. HFPV denotes high frequency percussive ventilation, LTV denotes low-tidal volume ventilation.

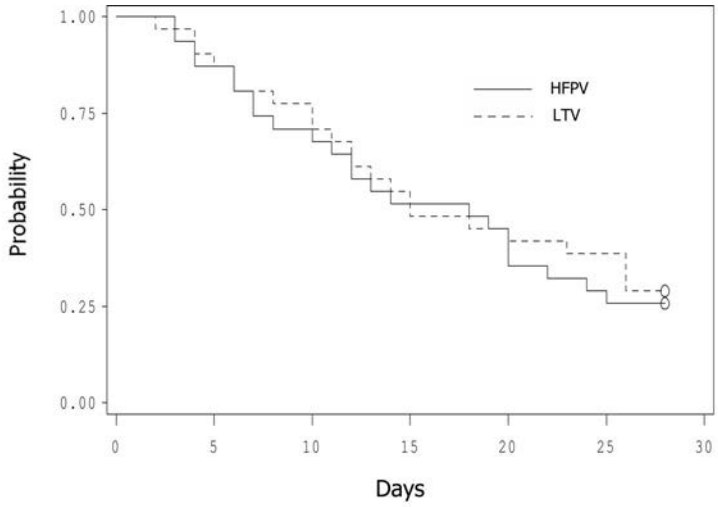
Figure 3. Comparison of immunoassays for interleukin (*IL*)-6 and IL-8 over 7 days after randomization.

complicates ventilator management. In animal models, it has been demonstrated that the major insult after inhalation injury is the obstruction and collapse of small airways leading to distal atelectasis and subsequent pneumonia (31). In addition, severe inhalation injury can result in an alveolar filling process that is characterized by diffuse alveolar damage consistent with ALI/ARDS (32).

Although ventilation was similar in both arms (Table 2), oxygenation, in the form of the ratio of Pa_{O_2} to F_{IO_2}, was significantly better in the HFPV arm over the first week after randomization (Fig. 2). Carman et al (33) reported similar findings in 64 children with severe burns and respiratory failure randomized to either HFPV or pressure-control ventilation (target tidal volume 6–8 mL/kg) by demonstrating improved oxygenation at lower peak airway pressures with HFPV. The fact that the ratio of Pa_{O_2} to F_{IO_2} was higher despite equivalent mean airway pressure and positive end-expiratory pressure settings and lower peak inspiratory pressures in the HFPV arm (Table 2) suggests that HFPV uses alternate mechanisms that augment gas exchange. These mechanisms, to include longitudinal dispersion, pendelluft, and molecular diffusion, have been previously described (9, 34, 35). It is important to note that early improvement in oxygenation may not be relevant or may be countered by long-term harm as evidenced by the ARDSnet trial in which the large tidal volume group appeared to have favorable results initially based on oxygenation parameters (13). Regardless, gas exchange goals were met in all subjects in the HFPV arm, whereas they were not in nearly one third of the LTV arm. Perhaps an alternate strategy is necessary to optimize LTV. It is well recognized that plateau pressure is not the best measure of estimating transalveolar pressure in this patient population when considering the various extrapulmonary contributors. A strategy guided by esophageal pressures may be a more effective approach when dealing with such a population. Talmor et al (36) demonstrated that a ventilator strategy using esophageal pressures to estimate transpulmonary pressure significantly improved oxygenation by allowing the use of higher levels of positive end-expiratory pressure.

Still, based on intent to treat, our primary outcome of ventilator-free days in the first 28 days was no different either by primary analysis or by log-rank test (Fig. 4). Neither were other clinically important outcomes such as mortality and VAP (Table 3). In our study, there was only a trend toward a lower incidence of VAP in the HFPV arm when compared with the LTV arm (32% vs. 53%, $p = .12$). The percussive effect generated by the flow-interrupted subtidal breaths in HFPV is thought to facilitate the evacuation of airway debris and mucous often abundant after inhalation injury (6). As such, HFPV has long been advocated as an important mode of ventilation in patients with inhalation (7, 37). The only prospective study published to date in adult burns had neither the power nor an adequate follow-up period to detect a difference in the incidence of pneumonia (12). Based on our results, setting $\alpha = 0.05$, a sample size of 110 patients in each arm would have been required to detect a difference in VAP with 80% power. A multicentered study would be necessary to attain these numbers in this population.

Despite the lack of a positive finding in many of our clinical outcome variables, we have demonstrated that an HFPV-based strategy is at least no more harmful than an LTV-based strategy. From an inflammatory standpoint, it appears that HFPV does not promote more cytokine release than a low-tidal volume strategy as evidenced by IL-6 and IL-8 levels over the first 7 days (Fig. 3). In fact, our results indicate that HFPV may even be more "lung-protective" than LTV when considering the 13% incidence of barotrauma over 28 days compared with 0% in the HFPV arm (Table 3). However, this finding should be counterbalanced by the occurrence of VATB in 6% of the HFPV group. Supplemental Figure 8 depicts this condition in one of the study subjects see Supplemental Fig. 8 [see Supplemental Digital Content 4, http://links.lww.com/CCM/A161]). VATB has been described previously as a condition that is likely to be secondary to inadequate humidification delivery (16). Allan et al (38) demonstrated that HFPV's distinct gas-flow mechanism can impair heating and humidification in the trachea.



*Kaplan-Meier curves on the probability to remain off mechanical ventilation over the 28 day study period. Log-Rank p-value for the difference between high frequency percussive ventilation (HFPV) and low tidal volume (LTV) is $p = 0.70$.

Figure 4. Kaplan-Meier curve depicting the probability of subjects remaining on mechanical ventilation over the 28-day study period.

Thus, testing and optimizing the humidification system is vital when using this mode of ventilation.

There is an important trend toward HFPV subjects requiring less sedation than LTV patients. This may be the result of the "inspiratory fail-safe" feature in the HFPV that permits spontaneous ventilation in both the inspiratory and expiratory phases (39). On the other hand, it may be that LTV is not well tolerated in this population, perhaps secondary to increased work of breathing (40) necessitating increased sedation. Still, this slight increase in sedation requirement in the LTV arm did not translate to a decrease in ventilator-free days.

Like in other single-center trials, a limitation is the presence of institutional bias. In our institution, many clinicians favored HFPV; this was manifested during the conduct of the trial in that three patients in the LTV arm were switched to HFPV off protocol based largely on attending preference. These subjects were continued on HFPV while the intent-to-treat principle was applied in our final analysis. Because of this, every effort was made to communicate to physicians, nurses, and respiratory therapists the importance of the proper conduct of this trial through annual and *ad hoc* training. In addition to these three patients, another 11 rescue patients (nine LTV, two HFPV) were placed on ventilator modes that they were not originally assigned to. This clearly clouds the interpretation of many of the end points. Another limitation is our small sample size. Still, this is the largest study in this population for this purpose to date, perhaps highlighting the difficultly faced by many investigators attempting clinical trials in niche populations. The recent establishment of a multicenter trials group among burn centers in North America may help assist in future collaborative studies to overcome these types of limitations (41, 42). Any future multicenter studies would have to take into account these preliminary findings and address the potential safety issues surrounding a low-tidal volume-based strategy in this population, particularly in those with inhalation injury.

In conclusion, we found that a strategy using LTV was inadequate to meet oxygenation and ventilation goals in a significant percentage of burn patients, especially in those with inhalation injury. Furthermore, we found no significant difference between HFPV and LTV with respect to the lung protection provided.

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